Estrogen plus progestin did not improve health-related quality of life in postmenopausal women 50 to 79 years of age

Hays J, Ockene JK, Brunner RL, et al. **Effects of estrogen plus progestin on health-related quality of life.** N Engl J Med. 2003;348:1839-54.

QUESTION

In postmenopausal women 50 to 79 years of age, is estrogen plus progestin (EPP) more effective than placebo for improving health-related quality of life (HRQL)?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, participants, data collectors, outcome assessors, and monitoring committee),* placebo-controlled trial with 1-year follow-up (Women's Health Initiative).

SETTING

40 U.S. clinical centers.

PATIENTS

16 608 community-dwelling postmenopausal women who were 50 to 79 years of age (mean age 63 y) and had an intact uterus. Exclusion criteria included a last menstrual period that occurred < 6 months before enrollment in the study (< 12 mo for women 50 to 54 years of age), predicted survival < 3 years, history of breast cancer, low hematocrit or platelet count, alcoholism, and dementia. Follow-up was 100%.

INTERVENTION

Women were allocated to EPP therapy (conjugated equine estrogen, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg once/d) (n = 8506), or placebo (n = 8102).

MAIN OUTCOME MEASURES

HRQL and functional status (RAND 36-Item Health Survey), depressive symptoms (Center for Epidemiologic Studies Depression Scale and the National Institute of Mental Health Diagnostic Interview Schedule), sleep disturbance (5-item Women's Health Initiative Insomnia Rating Scale), sexual functioning, cognitive functioning (Modified Mini-Mental State Examination), and menopausal symptoms.

MAIN RESULTS

Analysis was by intention to treat. Improvement from baseline in physical functioning, bodily pain, and sleep disturbance was greater in the EPP group than in the placebo group (Table). However, the improvements were small and not clinically meaningful (effect sizes were less than a threshold of 0.2 standard deviation units). The groups did not differ for all other outcomes.

CONCLUSION

In postmenopausal women 50 to 79 years of age, estrogen plus progestin was not more effective than placebo for improving health-related quality of life.

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*See Glossary.

Estrogen plus progestin (EPP) vs placebo in community-dwelling postmenopausal women at 1 year†

Outcomes (quality-of-life measures)	Mean change from baseline		Difference between groups (95% CI)
	EPP	Placebo	
Physical functioning (RAND 36-Item Health Survey scores)	−0.6	−1.4	0.8 (0.4 to 1.2)
Bodily pain (RAND 36-Item Health Survey scores)	0.1	−1.8	1.9 (1.3 to 2.5)
Sleep disturbance (WHI Insomnia Rating scale scores)	0.5	0.1	0.4 (0.2 to 0.6)

†WHI = Women's Health Initiative. Scores on the RAND 36-Item Health Survey subscales range from 0 to 100, with higher scores indicating better health or function; scores on the WHI Insomnia Rating scale range from 0 (worst) to 20 (best). CI calculated from data in article is defined in Glossary.

COMMENTARY

The large-scale trial by Hays and colleagues confirmed that we should not prescribe EPP therapy to postmenopausal women in the general population for prevention of chronic diseases (1) or for improvement of HRQL. However, 3 caveats of note exist when considering how the results may apply to our own postmenopausal patients.

First, the instruments used may not have been sensitive enough to measure menopause-related changes in HRQL over a year. The RAND 36-Item Health Survey is a generic instrument and was not specifically developed for menopause. Similarly, the depression scales used may not have been sensitive or specific enough to capture the mood swings and emotional lability of menopause. The question on sexual functioning asked women how satisfied or dissatisfied they were with their sexual function. Satisfaction depends on many factors, including a woman's relationship with her partner or lack thereof. In addition, the Modified Mini-Mental State Examination may have been too crude to detect change over a year.

Second, compliance was an issue with this trial. Noncompliance can dilute the results when data are analyzed according to the intention-to-treat principle. Even if EPP therapy did have a positive effect, the large number of women in the EPP group not taking the study pill would lower the effect in the whole treatment group and make it more difficult to show a difference between the treatment group and the placebo group.

Third, the women who participated in the study were willing to be randomized to either EPP or placebo. This group of women is probably different from those who would show up in our clinics seeking help with menopausal symptoms and would thus affect study generalizability.

Notwithstanding these caveats, the negative results together with the results of earlier trials (2, 3) force us to reexamine prescribing EPP therapy. Whether these results can be generalized to other hormone therapy regimens is unclear. Until we have further evidence, we should avoid prescribing EPP to postmenopausal women. There may be certain women with troubling menopausal symptoms who will be exceptions to this rule.

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References

1. **Rossouw JE, Anderson GL, Prentice RL, et al.** JAMA. 2002;288:321-33.
2. **Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA.** JAMA. 2002;287:591-7.
3. **Greendale GA, Reboussin BA, Hogan P, et al.** Obstet Gynecol. 1998;92:982-8.